

# Practical Applications of Insulin Pump Therapy in Type 2 Diabetes

Wendy Lane, MD

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## Summary

Type 2 diabetes has reached epidemic proportions in the U.S. As our population continues to get larger, more people develop the disease and require increasingly larger insulin doses for control. Continuous infusion of insulin via a pump can more closely mimic the natural secretion patterns of a normal pancreas. As this technology continues to evolve, more and more type 2 patients will be appropriate candidates.

## Key Points

- Type 2 diabetes is a costly disease.
- Prevalence is reaching epidemic proportions because of the weight problems in the U.S.
- Controlling glucose in patients with type 2 diabetes reduces complications.
- Oral antidiabetic agents will eventually fail to control the disease and insulin will be necessary.
- Insulin pumps are appropriate for many type 2 patients, especially those requiring large numbers of injections or doses per day.

TYPE 2 DIABETES IS A COSTLY DISEASE WITH a prevalence that is reaching epidemic proportions. Approximately 23.6 million Americans have diabetes with one third undiagnosed.<sup>1</sup> The lifetime risk for diabetes for a person born in 2000 is one in three. African Americans and Hispanic Americans have a two in five risk. For a Hispanic female, the risk is one in two.<sup>1</sup> Every 24 hours in the U.S., 4,384 new cases of diabetes are diagnosed.

The diabetes epidemic is being led by the obesity epidemic in the U.S. The risk of developing diabetes increases as body mass index increases.<sup>2</sup> Ninety percent of patients with type 2 diabetes are overweight or obese.<sup>3</sup>

Diabetes is an expensive disease, second only to mental health. Estimated total costs in 2007 were \$174 billion with direct medical costs accounting for \$116 billion and indirect costs at \$58 billion.<sup>1</sup>

Type 2 diabetes is one component of metabolic syndrome – a clustering of cardiovascular risk factors which put an individual at very high risk for heart disease (Exhibit 1). The underlying theme is insulin resistance. Insulin resistance is defined as subnormal biological response to any concentration of insulin in the blood whether it is endogenous or exogenous insulin. Early in type 2 diabetes, insulin resistance leads to a compensatory state of hyperinsulinemia.

Metabolic syndrome patients have a propensity to store fat around their middle in the visceral space – the liver particularly is floating in a sea of metabolically active fat. This fat leads to high levels of inflammatory cytokines and inflammation in the body which accelerates the process of atherosclerosis. Metabolic syndrome and type 2 diabetes leads to a prothrombotic state in which the patients are prone to form blood clots and have strokes and heart attacks.

Type 2 diabetes is equivalent to having heart disease. A patient with type 2 diabetes who have not had an event has the same risk of having a cardiovascular event as someone with diabetes who has already had a heart attack.

Every 24 hours in the U.S., 195 non-traumatic lower limb amputations secondary to diabetes are

### Exhibit 1: Components of the Metabolic Syndrome

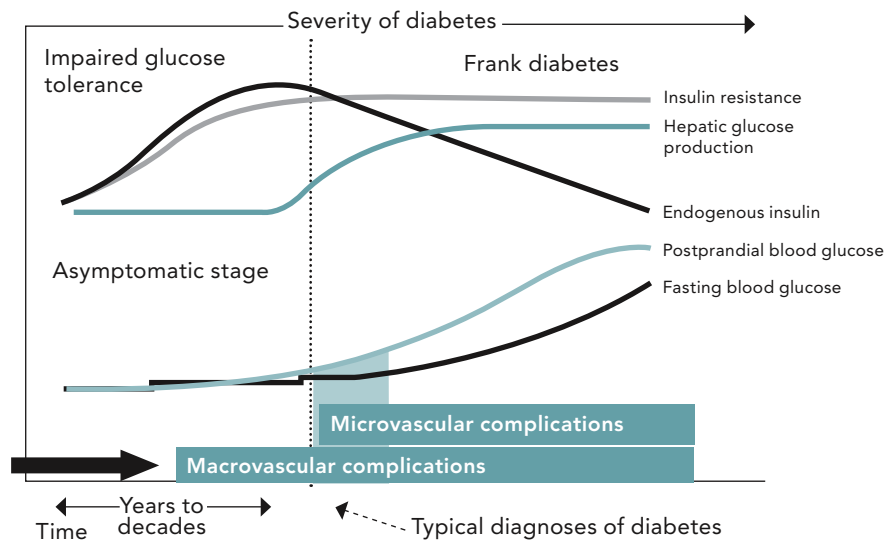
- Insulin Resistance/Hyperinsulinemia
- Central Obesity
- Hypertension
- Dyslipidemia (high trig; low HDL; small dense LDL)
- Procoagulant state (high fibrinogen and PAI-I)
- Endothelial dysfunction (albuminuria)
- Increased inflammation (CRP, TNF, cytokines)

### Exhibit 2: UKPDS Glucose Study Results<sup>5</sup>

A monotherapy approach, which achieved a median HbA difference of 0.9% (7.0% vs. 7.9%) over 10 years, reduced risk by:

		P
12%	any diabetes related endpoint	0.0029
16%	myocardial infarction	(0.052)
25%	microvascular disease	0.0099
21%	retinopathy at 12 years	0.015
33%	albuminuria at 12 years	0.000054

### Exhibit 3: Natural History of Type 2 Diabetes<sup>6</sup>



performed, and 128 people begin treatment for end-stage renal disease as a result of their diabetes.<sup>4</sup> Each 24 hours, 50 people develop blindness and 839 people die of diabetes or diabetes is a contributing cause of death.<sup>4</sup>

Preventing the complications of diabetes requires a multi-arm approach. This includes controlling blood glucose, blood pressure, lipids, and preventive strategies for other organs typically damaged by this disease. The UKPDS study provided evidence that controlling glucose in patients with type 2 diabetes reduces complications (Exhibit 2).<sup>5</sup>

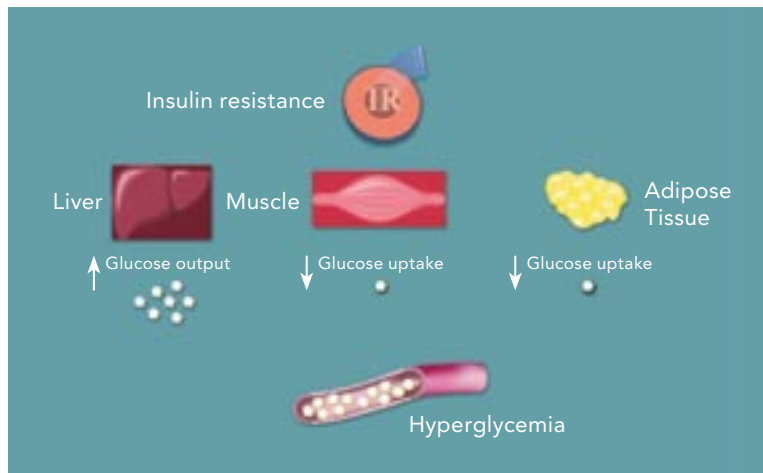
Type 2 diabetes is a progressive disorder that is asymptomatic in the early phases (Exhibit 3).<sup>6</sup> Im-

portantly the macrovascular complications of the disease begin during this asymptomatic phase before diagnosis occurs.

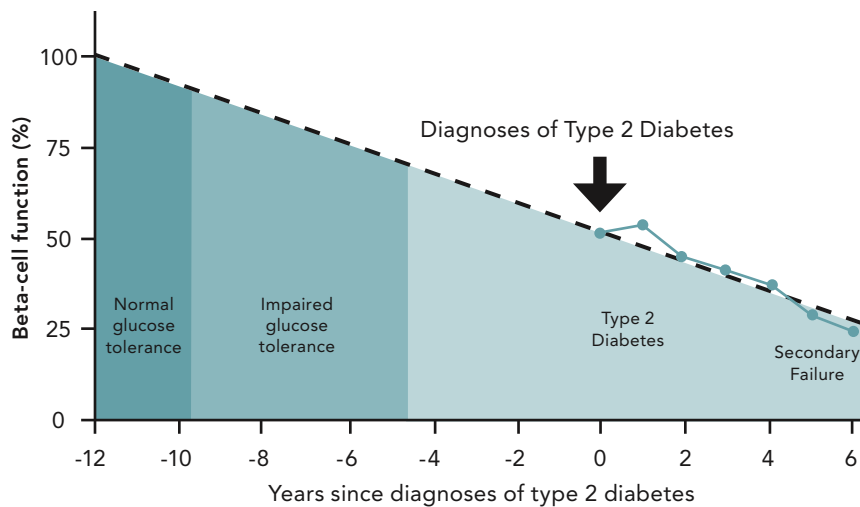
The consequences of insulin resistance at the tissue level include reduced glucose uptake into peripheral sites (i.e., fat and muscle, Exhibit 4). Combined with excessive glucose output by the liver, this leads to hyperglycemia. Skeletal muscle is the site for 80 percent of glucose utilization. When there is insulin resistance, essentially the patient cannot burn off any glucose they take in.

As type 2 diabetes progresses, glucose tolerance deteriorates as the pancreatic B cell function declines and less insulin is produced (Exhibit 5).<sup>7</sup> Af-

**Exhibit 4: Insulin resistance – reduced response to circulating insulin**



**Exhibit 5: Glucose Tolerance Deteriorates as Beta-Cell Function Declines<sup>7</sup>**



ter several years (the duration varies between individuals), oral agents which stimulate insulin release are no longer effective and supplemental insulin is required – the stage of “secondary failure”.<sup>5</sup> Five to ten percent of the patients treated with oral agents will have secondary failure every year. At 6 years, 50 percent of patients in the UKPDS were receiving insulin to maintain good glycemic control.<sup>5</sup>

Nonpharmacologic therapy is very important for type 2 diabetes management and many times get left by the wayside. Exercise, at least 45 minutes most days of the week, is very important for maintaining glucose control. Exercise and dietary changes should be maintained throughout the course of type

2 diabetes treatment. Both help make medications more effective. Oral agents are used after nonpharmacologic therapy alone is not enough. During the middle stages of the disease, combination therapy will be needed to control glucose. Late in disease, insulin therapy will be required.

As insulin deficiency progresses in the type 2 patient, a more physiologic multi-component insulin regimen will be needed to adequately replace normal insulin secretion. Insulin therapy is indicated if maximum tolerated dose of oral hypoglycemic agents fail to achieve glycemic targets. Other remediable factors should also be considered (e.g. food and exercise plan, oral medication adherence, intercurrent prob-

Exhibit 6: Basal-bolus insulin treatment: matching insulin administration to insulin needs<sup>8</sup>

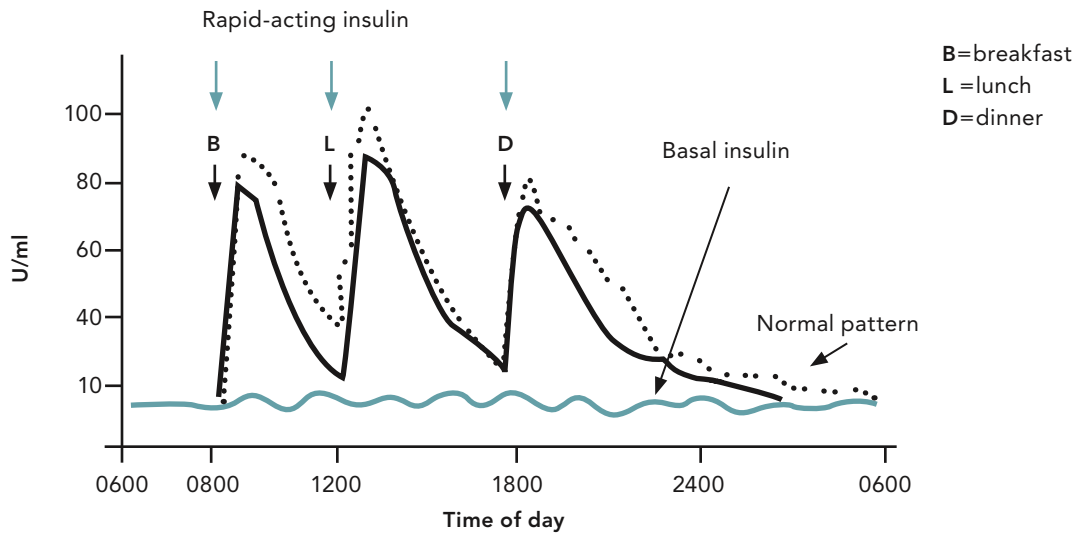
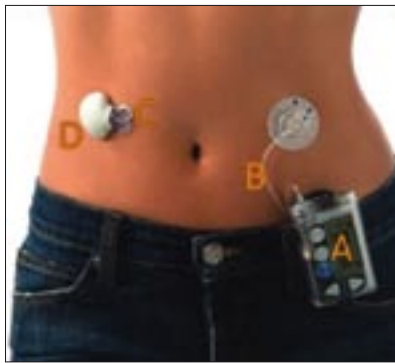


Exhibit 7



lems) before moving to insulin therapy.

Replacement of insulin, as close as possible to the pancreas' normal secretion, is desirable. To achieve this, there are two components of insulin therapy – basal and bolus. Basal insulin is insulin required to suppress hepatic glucose production in the fasting state. It controls fasting glucose levels. Bolus insulin is insulin required to maintain normal glucose disposal after eating and controls postprandial glucose levels. Long acting insulins such as insulin glargine and insulin detemer are used for basal dosing. Short acting insulins (insulin lispro, insulin aspart, and insulin glulisine) are used for bolus dosing and basal dosing when given as a continuous infusion.

Once insulin addition is necessary, basal insulin is usually added to oral agents to control fasting blood glucose. A long acting agent is given at bedtime. Rapid-acting insulin injections are then added se-

quentially at mealtimes to control postprandial glucose (“basal/bolus” regimen). Exhibit 6 illustrates both physiologic insulin secretion and an ideal basal and bolus dosing regimen of insulin.<sup>8</sup>

Intensive insulin regimens require at least four injections daily and may require up to seven injections. Many patients are unable to comply with this many injections. Additionally, patients may require very large insulin doses which can be painful.

Ways to better mimic physiologic insulin secretion and improve patient adherence lead to the development of insulin pumps. Exhibit 7 shows an insulin pump. The pump (A) contains a cartridge with a 2–3 day supply of insulin which is attached by flexible plastic canula to an infusion site (B). Many patients will also have a continuous glucose sensor (C & D). At this time, insulin pumps and continuous glucose sensors do not talk to each other. The patient has to make pump adjustments based on the sensor readings. Technology is moving toward a closed loop system where the pump will respond to the readings – an artificial pancreas.

Candidates for insulin pump therapy include people with inadequate glycemic control despite intensive multiple injection insulin regimen (with or without oral agents) who are motivated to improve blood glucose control and willing to frequently monitor continuous blood glucose readings. Many centers require patients to be willing to count carbohydrates to more accurately adjust their bolus doses. Pumps are also good for patients who need or desire more a flexible insulin delivery system to fit an active lifestyle, wish to avoid multiple insulin injections, or wish to minimize risk of hypoglycemia. The pumps

are also good for patients taking very large insulin doses. Single large doses of insulin are not well absorbed. The pump overcomes this problem by continuously infusing small amounts of insulin.

Pumps are appropriate for either type 1 or type 2 diabetes. Many payers, including Medicare, do not cover pumps for type 2 patients which may be a mistake.

There are four studies evaluating continuous subcutaneous insulin infusion versus multiple injection insulin in the type 2 diabetes population.<sup>9-12</sup> The results of these randomized control trials are mixed. Two trials showed no difference in hemoglobin A1C and two showed improvement. The differences seen within these studies may have been because of differences in baseline control. The patients in the positive studies had higher A1Cs and needed better control at baseline than the patients in the negative studies. These studies also took patients who had not had oral therapy intensified and switched them to pump therapy. Overall, based on the studies of insulin pumps in type 2 patients published so far, the more insulin deficient a patient is, the more they will benefit from a pump.

People with Type 2 diabetes who have tried both a pump and multiple daily insulin doses typically prefer the pump. Giving patients a treatment they are satisfied with is an important way to enhance compliance.

Patients with ever increasing obesity and very high levels of insulin resistance are requiring very high insulin doses (200 – 500 units/day). Delivery of these massive insulin doses is a problem for many providers and patients. One solution to this issue is the use of U-500 regular insulin, a very concentrated form of insulin. With this product, 1 cc contains 500 units of insulin rather than 100 units. This product has been used in pumps for patients who require 200 units or more per day. The only studies that have been published with this approach are small and nonrandomized.

One small study of U-500 insulin delivered by pump found that two of four patients' insulin requirements decreased once they were switched to the more concentrated form.<sup>13</sup> Improved absorption with the more concentrated form with a smaller infusion volume may have accounted for these changes. This report also found a significant savings with this approach. Another small study found that A1C decreased with the U-500 via pump approach without significant hypoglycemia or weight gain.<sup>14</sup> Although increasing insulin doses tend to lead to weight gain, another small study found that patients lost a modest amount of weight with concentrated insulin via pump therapy.<sup>15</sup>

## Conclusion

Insulin pumps are not just for Type 1 diabetics. Type 2 patients can benefit from insulin pump therapy. Delivery of very large doses of insulin is a problem that can be solved through the use of concentrated insulin via a pump. **JMCM**

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**Wendy Lane, MD** is Director of Clinical Research at the Mountain Diabetes and Endocrine Center in Asheville North Carolina.

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